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Nocturnal noninvasive ventilation in addition to rehabilitation in hypercapnic COPD patients

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ABSTRACT

Rationale: Long-term noninvasive positive pressure ventilation (NIPPV) might improve the outcomes of pulmonary rehabilitation in COPD patients with chronic respiratory failure.
Objective: To investigate whether nocturnal NIPPV in addition to pulmonary rehabilitation as compared to pulmonary rehabilitation alone improves health-related quality of life, functional status, and gas exchange in COPD patients with chronic hypercapnic respiratory failure.
Measurements: Seventy-two COPD patients were randomly assigned to nocturnal NIPPV in addition to rehabilitation (n=37) or rehabilitation alone (n=35). Before and after the 3-months intervention period outcome measures were assessed.
Results: The Chronic Respiratory Questionnaire total score improved 15.1 points with NIPPV + rehabilitation, compared to 8.7 points with only rehabilitation. The difference of 7.5 points was not significant ($p=0.08$). However, compared to rehabilitation alone, the difference in the fatigue domain was greater with NIPPV + rehabilitation (mean difference 3.3 points, $p<0.01$), as was the improvement in the Maugeri Respiratory Failure questionnaire total score (mean difference -10%, $p<0.03$) and its cognition domain (mean difference -22%, $p<0.01$). Furthermore, the addition of NIPPV improved daytime arterial carbon dioxide pressure (mean difference -0.3 kPa; $p<0.01$), and daily step count (mean difference 1269 steps/ day, $p<0.01$). This was accompanied by an increased daytime minute ventilation (mean difference 1.4 L; $p<0.001$).
Conclusion: Noninvasive ventilation augments the benefits of pulmonary rehabilitation in COPD patients with chronic hypercapnic respiratory failure as it improves several measures of health-related quality of life, functional status, and gas exchange.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide.[1] Due to the progressive nature of the disease, many patients will develop severe COPD and chronic respiratory failure. Once chronic respiratory failure is present, patients are often severely dyspnoeic at low exercise levels, their quality of life is reduced, and mortality rates are high.[2, 3]

In patients with severe COPD, pulmonary rehabilitation might be less effective, [4] as extreme breathlessness limits these patients in achieving high exercise intensities. Therefore, additive therapies, like noninvasive ventilation, are needed.

Nocturnal noninvasive ventilation might improve the outcomes of rehabilitation by resting the respiratory muscles,[5-7] improvement of the internal milieu of the respiratory muscles [8], improved lung mechanics,[9, 10] improved ventilation during the day,[11, 12] and improved sleep quality.[13]

Trials on noninvasive ventilation in stable COPD have yielded conflicting results.[5, 13-19] A recent meta-analysis did not show beneficial effects on daytime blood gases, lung function, respiratory muscle function, exercise tolerance and mortality.[20] The studies differed considerably in patient selection, the mode and duration of ventilation, ventilatory settings, and the degree of assistance and time to adjust to the ventilator.

Of all studies on noninvasive ventilation, only two studies have investigated it as an additional therapy next to pulmonary rehabilitation.[18, 21] One of these studies used negative pressure ventilation.[21] In the other study, in patients with mild respiratory failure, despite poor compliance with the ventilator, improvements in exercise tolerance and health-related quality of life were found with the addition of noninvasive positive pressure ventilation.[18]

We hypothesise that noninvasive intermittent positive pressure ventilation (NIPPV) in addition to pulmonary rehabilitation as compared to pulmonary rehabilitation alone improves health-related quality of life, functional status, and gas exchange in severe COPD patients with chronic hypercapnic respiratory failure.

METHODS

Patients

Patients were recruited from hospitals in the northern Netherlands. Inclusion criteria were: stable clinical condition (no exacerbation in the four weeks prior to study participation together with a pH>7.35); severe COPD (GOLD stage III or IV [22] (forced expiratory volume in 1 second (FEV_1)/ forced vital capacity < 70% and FEV_1 < 50% predicted); hypercapnia at rest (arterial carbon dioxide pressure ($PaCO_2$) > 6.0 kPa while breathing room air); and age between 40 and 76 years. Exclusion criteria were: cardiac diseases limiting exercise tolerance; neuromuscular or restrictive pulmonary diseases; previous exposure to chronic NIPPV or to a pulmonary rehabilitation program during the previous 18 months; or an apnoea/ hypopnoea index ≥ 10 / hour (online supplement).

The study was approved by the local Medical Ethical Committee. All participants gave written informed consent to participate. The study is registered at ClinicalTrials.Gov (ID NCT00135538).

Study design

The design of the study was parallel-group randomised, controlled. Patients were randomly assigned to nocturnal NIPPV in addition to rehabilitation (NIPPV + PR) or to rehabilitation alone (PR). Randomisation was computerised and performed by an independent statistician. To achieve an equal distribution of these parameters between the groups, the randomisation was performed with the minimisation method with factors for FEV_1 (≤ 1.2 L or > 1.2 L), arterial carbon dioxide pressure ($PaCO_2$) (≤ 7.0 kPa or > 7.0 kPa) and body mass index (≤ 30 kg/m^2 or > 30 kg/m^2).[23]

After randomisation, patients were maintained on their usual medication for a 12-week run-in period. Thereafter, the patients started a 12-week multidisciplinary rehabilitation program. The program consisted of strength training, cycling, walking, inspiratory muscle training, education, and psychological and/or nutritional support if necessary. Patients trained 3 times a week for 1 hour each session fully supervised.

In the PR + NIPPV group, immediately before starting the rehabilitation program, patients were instituted on nocturnal bilevel NIPPV (bilevel positive airway pressure (BiPAP), spontaneous/ timed mode (S/T), via nasal or full face mask) in the hospital. Inspiratory airway pressure (IPAP) was increased up to maximal tolerated pressure titrated towards an optimal correction of nocturnal arterial blood gases ($PaCO_2$<6.0 kPa and arterial oxygen pressure (PaO_2)>8.0 kPa). Effectiveness of NIPPV was monitored by means of nocturnal blood gas registrations at baseline before institution on NIPPV, at the end of the in-hospital period, and after the rehabilitation program.

Within one week before and after the rehabilitation program the following questionnaires and measurements were performed: the Chronic Respiratory Questionnaire (CRQ),[24] the Maugeri Respiratory Failure questionnaire (MRF-28),[25] the Severe Respiratory Insufficiency questionnaire (SRI),[26] the Hospital Anxiety and Depression Scale (HADS),[27] the Medical Research Counsel,[28] Borg scale,[29] arterial blood gases, 6-minute walking test, endurance shuttle walk test, incremental cycle ergometry, daily step count,[30] and lung function.

Details of the rehabilitation program, institution on NIPPV, and measurements used are given in the online repository.

Sample size

The primary outcome parameter was health-related quality of life as measured by the CRQ. To detect a clinically relevant change in CRQ score of 10 points with 80% power, at least 40 patients per group were needed.[31] Considering a probability of 20% drop-out of randomised patients, the target sample size was 50 patients per group.

Analyses and Statistics

Results were expressed as mean ± SD or median (interquartile range (IQR)). The main outcome parameters were evaluated in terms of patient completers. Outcomes were assessed in terms of changes from baseline (paired t-test or Wilcoxon signed rank test for separate groups) and differences in changes from baseline between the two groups corrected for baseline values (linear regression analysis). The Medical Research Counsel is a categorical scale, and therefore changes were compared to a chi-square distribution test to assess

differences in changes between groups. Overnight blood gas registration results were assessed by repeated measures ANOVA with post-hoc Bonferoni corrections. SPSS 14.0 was used for all analyses. A p-value < 0.05 was considered significant.

RESULTS

Patients

Eighty-seven patients of the approached 227 patients who met the inclusion criteria between September 2004 and January 2007, agreed to participate. As 15 patients eventually did not satisfy the inclusion criteria, 72 patients were randomised. During the run-in period, six patients randomised to the NIPPV + PR group dropped out (Figure 1).

Table 1. Baseline characteristics

Characteristics	NIPPV + rehabilitation	Rehabilitation
Subjects, n	31	35
Gender, M:F	18: 13	17: 18
Age, yrs	63 ± 10	61 ± 7.4
Patients on LTOT, n	14	16
In-hospital rehabilitation, n (%)	12 (39%)	17 (49%)
BMI, kg/m^2	27.1 ± 6.4	27.5 ± 6.3
Pack years, yrs, median (IQR)	42 (31-57)	43 (24-58)
CRQ dyspnoea	16 ± 4	17 ± 5
CRQ fatigue	14 ± 3	13 ± 5
CRQ emotion	32 ± 7	30 ± 8
CRQ mastery	19 ± 4	17 ± 5
CRQ total score	81 ± 15	78 ± 19

Legend table 1: Means ± SD or median (interquartile range, IQR) as indicated. Baseline blood gases, exercise tolerance, and lung function data are presented in table 2-4.
LTOT: long-term oxygen therapy; * changes in LTOT therapy were made in only 2 vs. 5 patients in the NIPPV + PR and PR group during the rehabilitation period (see online repository for detailed information), BMI: body mass index; CRQ: chronic respiratory questionnaire.

Treatment compliance

In the NIPPV + PR group, seven patients did not complete the study. Five patients could not adapt to the NIPPV (16%). One patient withdrew because of rheumatic complaints. One patient died of progressive respiratory failure due to a COPD exacerbation after 69 days on NIPPV, despite initial blood gas improvements. The completers used the NIPPV on average 96 % of the days with a median daily NIPPV use of 7.7 h (IQR 5.8 to 8.5 h/ day). In the NIPPV + PR group, non-completers had a lower FEV_1 (0.59 ± 0.17 vs.0.90 ± 0.38; $p<0.05$), lower vital capacity (2.20 ± 0.61 vs. 2.89 ± 0.82; $p<0.05$) and higher residual volume % of total lung capacity (69 ± 6 versus 62 ± 8; $p<0.05$) compared to completers.
In the PR group, three patients did not complete the study because of non compliance (9%). These patients had a higher total lung capacity (144 ± 3% versus 122 ± 19%) and residual volume (255 ± 10% versus 220 ± 64%) compared to the completers in this group ($p<0.01$).

The number of rehabilitation sessions attended was similar between the groups (NIPPV + PR group: 39 ± 4 versus PR group: 40 ± 4 sessions in the PR group (87% versus 89% of the prescribed sessions)). In both groups the target peak workload as prescribed in the rehabilitation protocol (140% of the peak work load at baseline cycle ergometry) was achieved (NIPPV + PR: 140 (57-500) % versus in the PR group: 140 (63-350) %).

NIPPV settings and overnight arterial blood gasses

Mean IPAP in the completers was 20 ± 4 cm H_2O. Mean expiratory airway pressure (EPAP) was 6 ± 2 cm H_2O. Mean respiratory rates on NIPPV was 18 ± 3 breaths/min, inspiration time 0.9 ± 0.2 seconds, rise time 1.2 ± 0.6 seconds. Ventilator settings used in the drop-outs were not different (IPAP 18 ± 1 and EPAP 5 ± 1). Most patients were ventilated through a full face mask (70%), the remaining through a nose mask. Mask choice was not different between the completers and non-completers. Using NIPPV, mean nocturnal $PaCO_2$ improved from 7.4 ± 1.1 kPa to 6.6 ± 0.7 kPa at the end of the in-hospital institution. After three months mean nocturnal $PaCO_2$ was 6.4 ± 0.6 kPa. Additional oxygen was titrated to achieve oxygen saturation ≥ 90%. Mean nocturnal PaO_2 remained unchanged.

Health-related quality of life, mood state, and dyspnoea

The difference in CRQ score change was not significantly different between groups (mean difference 7.5 points (i.e. 0.5 point/ question), 95% CI -1.0 to 16.0, p=0.08; Figure 2; Table 5 data supplement). The CRQ fatigue domain improved significantly more in the NIPPV + PR group as compared to the PR group. The MRF-28 total score and the MRF-28 cognition domain also improved significantly more with the addition of NIPPV. The NIPPV group improved on the SRI summary score as well as on five out of seven SRI subscales whereas the PR group improved on none of the SRI domains. Changes in SRI scores were not different between the two groups. The HADS and the MRC dyspnoea scale improved to a similar extent in both groups.

Daytime arterial blood gases

After three months therapy, the $PaCO_2$ in the NIPPV + PR group improved significantly more compared to the PR group (Table 2; Figure 3). The improvements in PaO_2 and bicarbonate levels were not significantly different between the two groups. The change in $PaCO_2$ after three months correlated with the baseline $PaCO_2$ ($r = 0.58$, $p<0.001$), and with the number of hours use of NIPPV/ day (rho = 0.44, p=0.04).

Table 2. Changes in arterial blood gases after 3 months therapy.

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
$PaCO_2$, kPa	N+R	6.89 ± 0.68	6.44 ± 0.69	-0.45	-0.32 (-0.6 to -0.1)[†]
	R	6.81 ± 0.81	6.71 ± 0.58	-0.10	
PaO_2, kPa	N+R	7.82 ± 1.03	8.26 ± 1.20	0.44	0.25 (-0.2 to 0.7)
	R	8.33 ± 1.25	8.33 ± 0.93	0.01	
HCO_3^-,mmol/L	N+R	29.2 ± 2.3	28.4 ± 2.4	-0.9	-0.7 (-1.8 to 0.4)
	R	29.4 ± 2.7	29.1 ± 1.8	-0.3	

Legend table 2: Means ± SD. N+R: NIPPV + rehabilitation group; R: rehabilitation group; $PaCO_2$: arterial carbon dioxide pressure; PaO_2: arterial oxygen pressure; HCO_3^-: bicarbonate. All assessments at daytime on room air at rest without NIPPV. †: denotes significant difference in change between groups.

Exercise tolerance

There was no significant difference between the groups in 6-minute walking test, endurance shuttle walking test, and maximal oxygen uptake at peak cycle exercise performance change. However, daily step count increased significantly more with NIPPV+ PR compared to PR (Table 3).

Table 3. Changes in exercise tolerance after 3 months therapy.

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
6MWD, m	N+R	318 ± 131	340 ± 119	22	2 (-19 to 23)
	R	304 ± 112	325 ± 108	22	
ESWT, sec	N+R	283 (232-503)	475 (295-1010)	166	103 (-69 to 276)
	R	327 (187-831)	449 (213-1042)	0	
Borg max	N+R	5.7 ± 2.3	4.4 ± 2.0	1.3	-0.8 (-1.8 to 0.1)
	R	5.3 ± 2.0	5.0 ± 2.2	0.3	
VO_2max, ml/ min/ kg	N+R	9.1 ± 2.4	9.8 ± 2.9	0.7	0.3 (-0.9 to 1.4)
	R	9.1 ± 2.7	9.5 ± 3.0	0.5	
Daily step count, steps/day	N+R	1893 (591-3773)	2799 (891 – 6135)	391	1269 (242-2296)†
	R	1680 (699-3538)	2093 (914-3155)	93	

Legend table 3: Means ± SD for 6MWD, Borg max, and PWR. Medians (interquartile ranges (IQR)) and median changes for ESWT and daily step count. N+R: NIPPV + rehabilitation group; R: rehabilitation group. 6MWD: 6-minute walking distance, ESWT: endurance shuttle walk test, Borg max: maximum Borg score at ESWT; VO_2max: maximal oxygen uptake at peak cycle exercise performance. †: denotes significant difference in change between groups.

Lung mechanics and breathing patterns

Daytime resting minute ventilation improved significantly more with NIPPV + PR compared to PR. The increased minute ventilation was attributable to an increase in tidal volume, as breathing frequency did not change. The NIPPV+ PR group improved in $P_I$max, but the difference between the groups was not significant (Table 4). The other lung function parameters remained unchanged in both groups.

Table 4: Changes in lung function and breathing patterns after 3 months therapy.

		Baseline	After Rehab	Change within group	Between group difference in change (95% CI)
FEV_1, L	N+R	0.90 ± 0.38	0.89 ± 0.39	-0.01	-0.04 (-0.1 to 0.1)
	R	0.78 ± 0.30	0.81 ± 0.29	0.03	
VC, L	N+R	2.89 ± 0.82	2.98 ± 0.89	0.09	-0.07 (-0.3 to 0.2)
	R	2.47 ± 0.73	2.62 ± 0.86	0.15	
TLC, % pred	N+R	125 ± 18	125 ± 18	0.2	0.1 (-5.5 to 5.7)
	R	123 ± 19	123 ± 16	0.4	
RV%TLC	N+R	62 ± 8	62 ± 10	-0.1	1 (-3 to 5)
	R	66 ± 10	64 ± 9	-2.2	
$P_I$max, kPa	N+R	5.0 ± 2.6	6.4 ± 2.3	1.44	0.8 (-0.2 to 1.8)
	R	5.3 ± 2.2	5.9 ± 2.3	0.5	
V_E, L/ min	N+R	9.8 ± 3.0	10.6 ± 3.1	0.8	1.4 (0.3 to 2.4) †
	R	9.0 ± 1.9	8.6 ± 2.3	-0.4	
V_T, ml	N+R	506 ± 144	560 ± 135	54	53 (-9 to 116)
	R	524 ± 129	519 ± 147	-6	
BF, breaths/ min	N+R	20 ± 5	19 ± 5	0.6	0.5 (-1.4 to 2.3)
	R	18 ± 4	17 ± 5	0.2	

Legend table 4: Means ± SD scores. N+R: NIPPV+ rehabilitation versus; R: rehabilitation alone. FEV_1: forced expiratory volume in 1 second; VC: vital capacity; TLC, % pred: total lung capacity as a percentage of predicted value; RV%TLC: residual volume as a percentage of TLC; $P_I$max: maximal inspiratory pressure. V_E: minute ventilation during quiet breathing, V_T: tidal volume during quiet breathing, BF: breathing frequency during quiet breathing. †: denotes significant difference in change between groups.

DISCUSSION

The present study shows that, although nocturnal NIPPV in addition to pulmonary rehabilitation as compared to rehabilitation alone did not improve our primary outcome (the CRQ total score), it did improve the CRQ fatigue domain, the MRF-28 total and its cognition domain score, daytime $PaCO_2$, and daily activity level in severe COPD patients with chronic hypercapnic respiratory failure. These improvements were accompanied by an increase in daytime resting minute ventilation. We found no significant improvements in pulmonary function, exercise testing, dyspnoea, anxiety, and depression with the addition of NIPPV to pulmonary rehabilitation.

We found an improvement in $PaCO_2$ in the NIPPV group, which is in contrast to results from Garrod and colleagues who also studied NIPPV added to PR.[18] The lack of effect on blood gases in their study could very well be due to the low median NIPPV use of 2.08 h/day, lower median IPAP of 16, and the inclusion of patients with mild chronic respiratory failure (mean $PaCO_2$ 6.0 kPa). Finally, the effects of NIPPV on arterial blood gases were not carefully monitored and no target was defined for improvement in blood gases under NIPPV.
We adjusted ventilator settings based on nocturnal arterial blood gas registrations. On average, we used higher inspiratory pressures than previous randomised controlled trials have reported. However, in our study, there was no relationship between the height of the IPAP

(r=-0.04) or the inspiratory pressure difference (IPAP-EPAP; r=0.01) and the change in $PaCO_2$ after three months. This was consistent with our nocturnal registrations where we noticed that although a certain IPAP level is necessary to achieve effects, further increasing the IPAP does not always result in improvement in blood gases. This emphasises the importance of careful and reliable monitoring during institution of NIPPV. Our patients were instituted in hospital and carefully monitored. Drop-out rates were acceptable compared to other studies [13, 15] and ventilator use was high. The fact that compliance is important is confirmed by the relationship we found between the number of hours the NIPPV was used per night and the improvement in daytime gas exchange.

Improvement in health-related quality of life was the primary goal of our study. Although we did not find a significant effect on CRQ total score (our primary end-point), we did find significant improvements in the CRQ fatigue domain, the MRF-28 total score, and its cognition domain. Therefore it seems that adding NIPPV to pulmonary rehabilitation can improve health-related quality of life. Only a few studies investigated the effects of NIPPV on health-related quality of life.[5, 13, 18] When comparing our study to previous ones, it is important to acknowledge that our control PR group improved on HRQoL and exercise tolerance, while in two other studies the control group deteriorated.[5, 13] Furthermore, the improvement in CRQ total score that Garrod et al found with NIPPV+PR might have been influenced by the very low baseline CRQ scores especially in their NIPPV + PR group, despite the fact that the patients did not have very severe COPD.[18]
In our study, on average, the NIPPV group had a clinically relevant improvement of >0.5 point/item [31] on all CRQ domains and the CRQ total score, while the rehabilitation group improved clinically relevant only on the mastery domain.
We found associations that suggest a relationship between improvement in gas exchange and HRQoL (change in HCO_3^- vs. change in both the SRI total score (r= 0.46; p=0.001) and CRQ total score (r= -0.30; p=0.03) [32]; and change in $PaCO_2$ vs. change in MRF-28 cognition domain (r =0.51 (p=0.01)).

In contrast to the exercise tests, unsupervised daily step count did improve significantly more with NIPPV + PR compared to PR alone. An increase in daily step count was found before, but in a mixed group of patients with chronic respiratory failure.[33] The increase in daily step count did not correlate with $PaCO_2$ change, nor did it correlate with change in breathlessness scores, formal exercise test scores, or activity domains of the quality of life questionnaires. This reflects the fact that the pedometer provides a reflection of daily submaximal activity, not measured with exercise tests or questionnaires, but especially clinically relevant for the individual patient. Probably step count is an extension of endurance capacity. Furthermore, ESWT change tended to improve with NIPPV, but did not reach statistical significance, because of large spread in outcome.

The present study has some limitations. We did not use sham-ventilation in our control group, and so patients and investigators were not blinded to the therapy. We believe sham-ventilation is difficult to implement at home during the long period of this study. Secondly, we only included 72 patients while power calculation had provided that 40 versus 40 patients were needed to find a 10-point change in CRQ total score. However, recruitment was tedious and due to financial constraints we were unable to further extend the inclusion period. This might have influenced our results due to a type-II error for false negative outcomes. Effects that were already significant in our study with lower numbers of patients, however, remain valid (type I error unchanged set at 0.05). In contrast to the CRQ, the MRF-28 and SRI were developed especially for patients with chronic respiratory failure and contain items on

problems that patients with chronic respiratory failure experience. Both new questionnaires proved to be reliable, valid,[34] and more responsive in this patient group [35]. Therefore, powering on them might have been more appropriate. However, there was little experience with this questionnaire the moment our study was designed. Finally, we presented a fairly large number of outcomes. From a statistical point of view, presenting many outcomes would increase the chance of finding positive outcomes. However, omitting these important outcomes would raise questions about how they change with the addition of NIPPV. Furthermore, as expected outcomes (such as the different subscales of HRQoL) all changed in the same positive direction, we believe that these outcomes are in fact true.

In conclusion, noninvasive ventilation augments the benefits of pulmonary rehabilitation in COPD patients with chronic hypercapnic respiratory failure as it improves several measures of health-related quality of life, functional status, and gas exchange. We found that NIPPV acceptance rates were high as was the median number of hours use when careful assistance and monitoring were applied.

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Competing interests: None

FIGURE LEGENDS

Figure 1: Flow diagram of the study progress

Figure 2: Mean changes (+ SEM) in health-related quality of life scores after 3 months therapy in the NIPPV + rehabilitation group (black bars) versus the rehabilitation group (white bars)
Legend figure 2: Chronic Respiratory Questionnaire (CRQ) contains the domains dyspnoea, fatigue, emotion, and mastery; Maugeri Respiratory Failure questionnaire *(*MRF-28) contains the domains: daily activities (daily), cognition (cog), invalidity (inv); Severe Respiratory Insufficiency (SRI) questionnaire contains the domains respiratory complaints (RC), physical functioning (PF), attendant symptoms and sleep (AS), social relationships (SR), anxiety (AX), psychological well-being (WB), social functioning (SF). MCID: minimal clinically important difference.
†: denotes significant difference in change between groups (CRQ fatigue: mean difference in change between groups 3.3 points or 0.8 point/ question, 95% CI 0.8 to 5.7; MRF-28 cognition mean difference in change between groups -22%, 95% CI -35 to -9; MRF-28 total score mean difference in change between groups -10%, 95% CI -18 to -1).

Figure 3: Individual changes (dotted grey lines) and mean ± SD of the changes in $PaCO_2$ in NIPPV + rehabilitation group (N+R, left ■) and rehabilitation (R, right ♦) group after 3 months therapy.
Legend figure 3: N+R: NIPPV + rehabilitation group; R: rehabilitation group; †: the improvement in $PaCO_2$ in the NIPPV + rehabilitation group was also significantly different from the change in the rehabilitation group.

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SUPPLEMENTAL FILE FOR ONLINE REPOSITORY

Nocturnal non-invasive ventilation improves outcomes of rehabilitation in hypercapnic COPD patients

Marieke L. Duiverman, Johan B. Wempe, Gerrie Bladder, Désirée F Jansen, Huib A.M. Kerstjens, Jan G. Zijlstra, Peter J. Wijkstra.

METHODS

Patients

An overnight polygraphy (Embletta pds, Medcare Automation BV, Amsterdam, the Netherlands) was performed in patients with a body mass index ≥ 30 kg/m^2, in patients who snored or had complaints of disrupted sleep, excessive daytime sleepiness, or morning headache. Patients were excluded if the apnoea/ hypopnoea index was ≥ 10 episodes / hour. Of all 87 patients assessed for inclusion, a polygraphy was performed in 32 patients. The reason for performing the polygraphy was a BMI ≥ 30 in 25 patients, while a BMI <30 but complaints was the reason in seven patients. As shown in figure 1, 15 patients did not meet the inclusion criteria. In five of these 15 patients a polygraphy was performed. Four of them had an AHI-index> 10 and this was the reason for exclusion (median AHI-index 17.9 (range 15.0- 60.0 episodes/ hour)). The other 11 patients were excluded before because of an FEV_1>50% predicted or a PCO_2 < 6.0 kPa, cardiovascular disease, or an inability to fill in the questionnaires. Of the remaining 72 patients, a total of 16 patients dropped out (Figure 1). Of them, a polygraphy was performed in 4 patients (median AHI-index 3.2 (range 2.4- 6.0 episodes/ hour)). In the 56 completers, a polygraphy was performed in 23 patients (median AHI-index 2.0 (range 0.0- 9.8 episodes/ hour)).
Patients were excluded if medical history revealed significant cardiac diseases limiting exercise tolerance.
Therapy with long-term oxygen and medication was optimised during the intervention period by the pulmonary physician of the patient who was not involved in the study. Of the completers, 27 patients used long-term oxygen (LTOT) at baseline at a median flow rate of 1.5 L/min (range 0.5-3.0 L/min), at a median duration of 24 h/day (range 6-24 h/day). After 3 months, 32 patients were on LTOT, as 2 patients in the NIPPV+PR group and 4 patients in the PR group were prescribed LTOT during the rehabilitation period, while in one patient in the PR group LTOT was withdrawn because her resting PaO_2 without oxygen was 8.3 kPa. There were no significant differences in HRQoL scores between the patients on LTOT and the patients not on LTOT at baseline except for a higher MRF invalidity score in the LTOT patients (76 ± 28 % versus 57 ± 31%). Changes in HRQoL scores were not different except for a greater change in SRI physical functioning score in the patients not on LTOT (+ 6 ± 11 versus -3 ± 15 %). All arterial blood gas analyses were performed on room air without oxygen or ventilation.
At baseline, of the completers, 48 patients (86%) used inhaled corticosteroids, 26 patients (46%) used oral corticosteroids, 45 patients (80%) were on inhaled beta-agonist, 52 patients (93%) on anticholinergic medication, and 13 patients (23%) were on theophyllin. During the intervention period, in 3 PR patients, inhaled corticosteroids were started, in 1 PR patient oral steroids were started, in 3 PR patients beta-agonists were started, and in 2 PR patients anticholinergics were started. Additional changes in dose regimes were made by the patient's own pulmonologist.

Rehabilitation program

The participants followed a centre-based rehabilitation program of twelve weeks. The program could be followed in-hospital or as an out-patient, depending on travel distance to the centre. Nine rehabilitation centres in the northern part of the Netherlands participated. The program started with a 3-week period of upper and lower limb strength exercises (Enraf-Nonius, Rotterdam, the Netherlands), three times a week.[1] Thereafter, the program

continued with nine weeks cycling (Lode medical technology, Groningen, the Netherlands; Tunturi, Almere, the Netherlands), walking, and inspiratory muscle training (Threshold® IMT, Respironics**,** Murrysville, PA, US). The cycling was performed two times a week for thirty minutes according to an interval-based protocol.[2, 3]. This cycling protocol consisted of alternating 1 minute loaded cycling (aimed at 140% of a patients initial peak work rate on cycle ergometry), and 1 minute unloaded cycling, during a total of thirty minutes. Walking was performed twice a week. Initially patients walked ten minutes per session. Walking time was increased with five to ten minutes every week until the patients were able to walk thirty minutes per session. The speed of walking was adjusted in order to achieve a maximum Borg score of approximately 80% of the maximum Borg score at the initial six minute walking test. Inspiratory muscle training was performed on an inspiratory threshold device thirty minutes a day on an interval basis (2 minutes loaded breathing, followed by 1 min rest). The aim was to start with the threshold resistance on 30% of baseline maximal inspiratory pressure ($P_I$max). The resistance was increased with 5-10% per session until 70% $P_I$max was reached.[4, 5] Oxygen was used during training to maintain arterial oxygen saturation >92%. Twenty-nine patients used oxygen during the training (16 in PR group and 13 from NIPPV+PR group). The patients also participated in group education sessions where information was given about the disease, various strategies of treatment, use of medication, ways of coping with the disease, the role of rehabilitation, and how to recognise an exacerbation. Next to this, patients were taught breathing exercises, e.g. training lip-pursing techniques, expiratory abdominal augmentation, and synchronisation of thoracic and abdominal movement. Finally, patients received nutritional counselling by a dietician and, if necessary, psychosocial support.

NIPPV

Patients randomised to the NIPPV + rehabilitation group were instituted on NIPPV at the University Medical Center Groningen. They were hospitalised within a week after the baseline measurements and before the rehabilitation program started.
Non-invasive ventilation was supplied through a pressure cycled ventilator, applying both inspiratory and expiratory pressure to the patient (BiPAP; Synchrony, Respironics, INC., Murrysville, PA, USA). A nasal or full face mask (Mirage mask, ResMed Ltd, UK) of the proper size was used. The ventilator was set in a spontaneous/ time mode (S/T), with a backup frequency. We started with an inspiratory positive airway pressure (IPAP) of 12 cm H_2O and an expiratory positive airway pressure (EPAP) of 4 cm H_2O. IPAP was increased until the maximal tolerated pressure was achieved and titrated towards an optimal correction of arterial blood gases during the night ($PaCO_2$<6.0 kPa and a PaO_2>8.0). EPAP was titrated on patient comfort. Ventilator breathing frequency was adjusted to the patient's own spontaneous breathing frequency. If needed, O_2 was added to the ventilatory circuit to obtain a saturation of ≥ 90%. A humidifier (HC 150 Fisher & Paykel Healthcare, Australia) was used if needed. To monitor effectiveness of the NIPPV, nocturnal arterial blood gas registrations were performed in the intensive care unit at baseline before institution on NIPPV, after the practice period, and after three months. An arterial canula was placed in the a. radialis and arterial blood gas samples were taken every two hours. For analyses we used the mean of at least three samples taken when patients were asleep.
Initially, patients were hospitalised to practice NIPPV use under close supervision of a nursing consultant specialised in home mechanical ventilation. The in-hospital practice period lasted until patient could sleep at least six hours with the NIPPV (mean number of days necessary in our patients 5.0 ± 0.6 days). When a patient was able to sleep at least 6 hours per night with the ventilator, the second arterial blood gas registration was performed. If this gave satisfactory results, the patient went home with their ventilator. On the first day a home visit

was done by a specialised nursing consultant of the home mechanical ventilation centre, who supervised the ventilatory support during the whole study period. Ventilator compliance was determined from the ventilator counter readings.

Measurements

The following measurements were performed at baseline and after the 3-months intervention period.

Health-related quality of life

The primary outcome parameter was health-related quality of life, assessed by the interviewed version of the Chronic Respiratory Questionnaire (CRQ).[6] In addition, health-related quality of life was measured with the Maugeri Respiratory Failure questionnaire (MRF-28),[7] and the Severe Respiratory Insufficiency questionnaire (SRI).[8]

We used the interviewed version of the Chronic Respiratory Questionnaire (CRQ). It contains 20 items divided into four dimensions: dyspnoea, fatigue, emotion, and mastery. The CRQ total scores range from 20 to 140, with higher scores indicating better HRQoL. Physical function is assessed by asking the patients to quantify their dyspnoea during 5 frequently performed activities in daily life. They are asked to choose 5 activities from a list of 25 activities or they can mention activities not on the list. The CRQ dyspnoea domain scores range from 5 to 35. Physical function is also assessed by 4 items related to fatigue and energy level. The CRQ fatigue domain scores range from 4 to 27. Emotional function, including the emotion and mastery dimensions, includes questions about frustration, depression, anxiety, panic, and fear for dyspnoea. The CRQ emotion domain scores range from 7 to 49, those of the mastery domain range from 4 to 28.

The MRF-28 consists of 3 separate domains and a total score [7]. The daily activities domain contains 11 items related to dyspnoea during daily activities and impairments in daily activities. The cognition domain contains 4 items related to memory function, attention and concentration tasks. The invalidity domain contains 5 items on self-image, social functioning and relationships. Furthermore, the total score contains additional items related to fatigue, depression and problems with treatment, giving a total of 28 items. Scores are coded as 1 (patient agrees with the item) or 0 (patient does not agree). Scores are than recalculated as a percentage of items with which the patient agrees. MRF-28 scores range from 0-100, with higher scores indicating worse HRQoL [7].

The SRI contains 49 items divided in 7 subscales related to respiratory complaints (8 items), physical functioning (6 items), attendant symptoms and sleep (7 items), social relationships (6 items), anxiety (5 items), psychological well-being (9 items), social functioning (8 items), and a summary scale. Items are scores from 1 to 5, 35 items are then recoded, and the mean score is calculated to a percentage. SRI scores on each domain and the summary scale range from 0-100, with higher scores indicating better HRQoL [8].

Mood state

The hospital anxiety and depression scale (HADS) was used to assess mood state. It contains 7 items assessing anxiety and 7 items assessing depression [9]. Scores per item range from 0 (no anxiety/ no depression) to 3 (maximal anxiety/ depression). Separate anxiety and depression scores (ranging from 0-21) were obtained.

Dyspnoea

Dyspnoea was assessed by the Medical Research Council.[10] The MRC is a 5-point scale (1: only dyspnoeic during heavy exercise; 5: too dyspnoeic to leave the house) containing items on various physical activities that precipitate dyspnoea. Patients were instructed to read the descriptive statements and then select the statement which fitted best. Furthermore, prior to and during the exercise tests the subjects were asked to estimate dyspnoea intensity, using a 10-point modified Borg scale.[11]

Exercise tests

6-minute walking distance
A 6-minute walking test was performed indoors, along a 40-meter flat, straight corridor, with the turnaround point marked with a cone. All patients had performed a practice test during the run-in period. Patients used their usual walking aids and, if applicable, their usual ambulatory oxygen therapy during the test. The test assistant gave standardised encouragements every 30 seconds and told the patient after 2 and after 4 minutes that he/she was 2 and 4 minutes on his/her way.[12, 13]

Shuttle walk tests
All patients first performed an incremental shuttle walk test.[14] From this, endurance shuttle walk speed was determined according to the protocol of Revill.[15] First, maximal oxygen uptake (VO_2max) was calculated (VO_2max= (0.85*(4.19+0.025*incremental shuttle walk distance [14]). Thereafter, the correct endurance walking speed was read from the graph of endurance walking speed against VO_2max as presented by Revill.[15]
For both tests, a practice walk was done during the run-in period. Both tests were performed on a 10 m shuttle course on a quiet flat corridor, demarcated by cones inset 0.5 m from either end to compensate for turning points. Patients were instructed to walk along the course, turning around the cones at either end in synchronization with the audio signals from the cassette player. Prior to the test, patients were given standardized instructions about the tests and instructions to continue walking until too tired or breathless to continue. During the tests, the test operator sat alongside the course and no encouragements were given.
For the incremental shuttle walk test the modified protocol of Singh was used.[14] Each minute the walking speed was increased by 0.17 m/s, so that the patient was required to walk progressively faster. The end of the test was determined by a) the patient, when to exhausted to maintain the required speed; b) the operator, if the patients failed to reach the cone by > 0.5 m for a second time.[14]
For the endurance shuttle walk test, the same course was used. The test started with a "warm up" slower pace, which lasted for approximately 100 s, preceded the endurance speed to enable the patient to practice walking around the shuttle course. Thereafter the actual endurance speed started and remained constant for the whole test. The test ended if the patient indicated that he was too tired or too breathless to continue or if the cut off time at 20 minutes, chosen for practical reasons, was reached. However, patients were unaware of any time limit and were discouraged from estimating how long they had been walking. The patients performed the endurance shuttle walk test twice at baseline to exclude learning effects.[15] The better of these two tests was used for analyses.

Cycle ergometry
The bicycle tests were performed between 4 to 8 hours after switching from NIPPV to spontaneous breathing. Prior to the bicycle test, all patients received 400 microgram salbutamol to achieve optimal bronchodilatation.

First, daytime resting arterial blood gases on room air were taken from all patients while lying (Rapid lab type 865, Siemens, U.S.A.).
An incremental bicycle ergometry was performed using a 1-min incremental protocol. Patients were seated on the bicycle, respired through a mouthpiece and wore a nose clip during the test. During the whole test minute ventilation, tidal volume, breathing frequency, and oxygen uptake were measured continuously (Oxycon Pro, Viasys, Bilthoven, the Netherlands). First, recordings were made during breathing at rest for five minutes. The average values of these five minutes were used to analyse resting breathing patterns.
The exercise test started with 1 min unloaded pedalling at 60 cycles/min. This was followed by a 1-min incremental protocol at five watt load increment/min, until the patient reported exhaustion. The maximum workload was defined as the highest work level reached and maintained for a least thirty seconds.

Activities of daily living

Daily physical activity was assessed on a performance basis by the Digiwalker SW-200 (Yamax; Tokyo, Japan).[16-18] This pedometer has proved to accurately detect steps taken, as an indication of volume of daily physical activity.[16, 17, 19] It has also shown evidence of reliability and convergent and discriminative validity.[18] In this study, patients were instructed to wear the pedometer during ten days (until going to bed), and to record the number of steps per day. Steps/day was expressed as step equivalents.

Lung Function

All patients performed lung function testing post bronchodilatation with 400 microgram salbutamol. Vital capacity and forced expiratory volume in 1 second (FEV_1) were obtained by spirometry according to ERS criteria.[20] Out of a least three technically correct measurements, the highest value of at least two reproducible values was used (with ≤150 ml difference between those two measurements). Lung volumes, total lung capacity, functional residual capacity and residual volume, were measured by body plethysmography.[21] Furthermore, maximal inspiratory pressure ($P_I max$) was measured at residual volume after maximal expiration. The $P_I max$ manoeuvre was repeated at least five times with one minute rest between the measurements until 3 readings were obtained with less than 10% variance between the measurements. Pressures had to be maintained at least 1 second (Masterscreen PFT, Viasys, Houten, the Netherlands).[22]

RESULTS

Table 5. Changes in health-related quality of life scores after 3 months therapy

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
Chronic Respiratory Questionnaire					
Dyspnoea, points	N+R	16.0 ± 4	19.1 ± 6	3.1	0.2 (-3.2 to 3.2)
	R	17.2 ± 5	19.5 ± 6	2.3	
Fatigue, points	N+R	13.8 ± 4	18.8 ± 4	5.0	3.3 (0.8 to 5.7) †
	R	13.6 ± 5	15.4 ± 6	1.8	
Emotion, points	N+R	32.6 ± 7	36.3 ± 6	3.7	2.4 (-0.9 to 5.5)
	R	30.7 ± 8	32.8 ± 8	2.1	
Mastery, points	N+R	19.3 ± 5	22.5 ± 4	3.3	1.5 (-0.4 to 3.4)
	R	17.8 ± 5	20.3 ± 5	2.5	
Total, points	N+R	81.7 ± 16	96.8 ± 15	15.1	7.5 (-1.0 to 16.0)
	R	79.3 ± 19	87.9 ± 20	8.7	
Maugeri Respiratory Failure Questionnaire					
Daily activities, %	N+R	58.9 ± 35	53.4 ± 29	-5.5	-5.3 (-17 to 6)
	R	55.7 ± 30	56.8 ± 27	1.1	
Cognition, %	N+R	50.0 ± 33	28.3 ± 25	-21.7	-22.0 (-35 to -9) †
	R	35.2 ± 39	40.6 ± 38	5.5	
Invalidity, %	N+R	67.0 ± 33	57.4 ± 33	-9.6	-6.1 (-19 to 7)
	R	65.0 ± 30	61.9 ± 36	-3.1	
Total, %	N+R	55.3 ± 24	44.6 ± 22	-10.7	-9.7 (-18 to -1) †
	R	52.2 ± 24	52.1 ± 24	-0.1	
Severe Respiratory Insufficiency Questionnaire					
Respiratory complaints, %	N+R	49.0 ± 17	58.7 ± 13	9.6	6.0 (-0.6 to 12.0)
	R	48.1 ± 17	52.1 ± 17	-4.1	
Physical functioning, %	N+R	40.9 ± 18	40.9 ± 21	0	-2.3 (-9.7 to 5.1)
	R	39.3 ± 17	42.0 ± 18	2.6	
Attendant symptoms and sleep, %	N+R	60.4 ± 19	71.1 ± 16	10.7	7.4 (-0.6 to 15.3)
	R	54.6 ± 18	60.2 ± 20	5.5	
Social relationships, %	N+R	58.4 ± 17	64.5 ± 13	6.1	1.0 (-5.6 to 7.6)
	R	63.3 ± 16	65.5 ± 14	2.2	
Anxiety, %	N+R	54.8 ± 23	63.3 ± 17	8.5	3.1 (-5.1 to 11.3)
	R	50.7 ± 20	56.9 ± 22	6.1	
Well-being, %	N+R	63.0 ± 19	68.1 ± 14	5.1	4.2 (-2.5 to 10.9)
	R	54.9 ±20	58.8 ±19	3.9	
Social functioning, %	N+R	50.3 ± 21	54.1 ± 16	3.7	1.1 (-6.4 to 8.6)
	R	51.6 ± 20	53.6 ± 18	2.0	
Summary score, %	N+R	53.8 ± 15	60.1 ± 11	6.3	3.1 (-2.0 to 8.2)
	R	51.8 ±14	55.7 ±15	3.8	

Legend table 5: Means ± SD scores. N+R: NIPPV+ rehabilitation versus R: rehabilitation alone. *: denotes significant change from baseline to 3 months within the group; †: denotes significant difference in change between groups.

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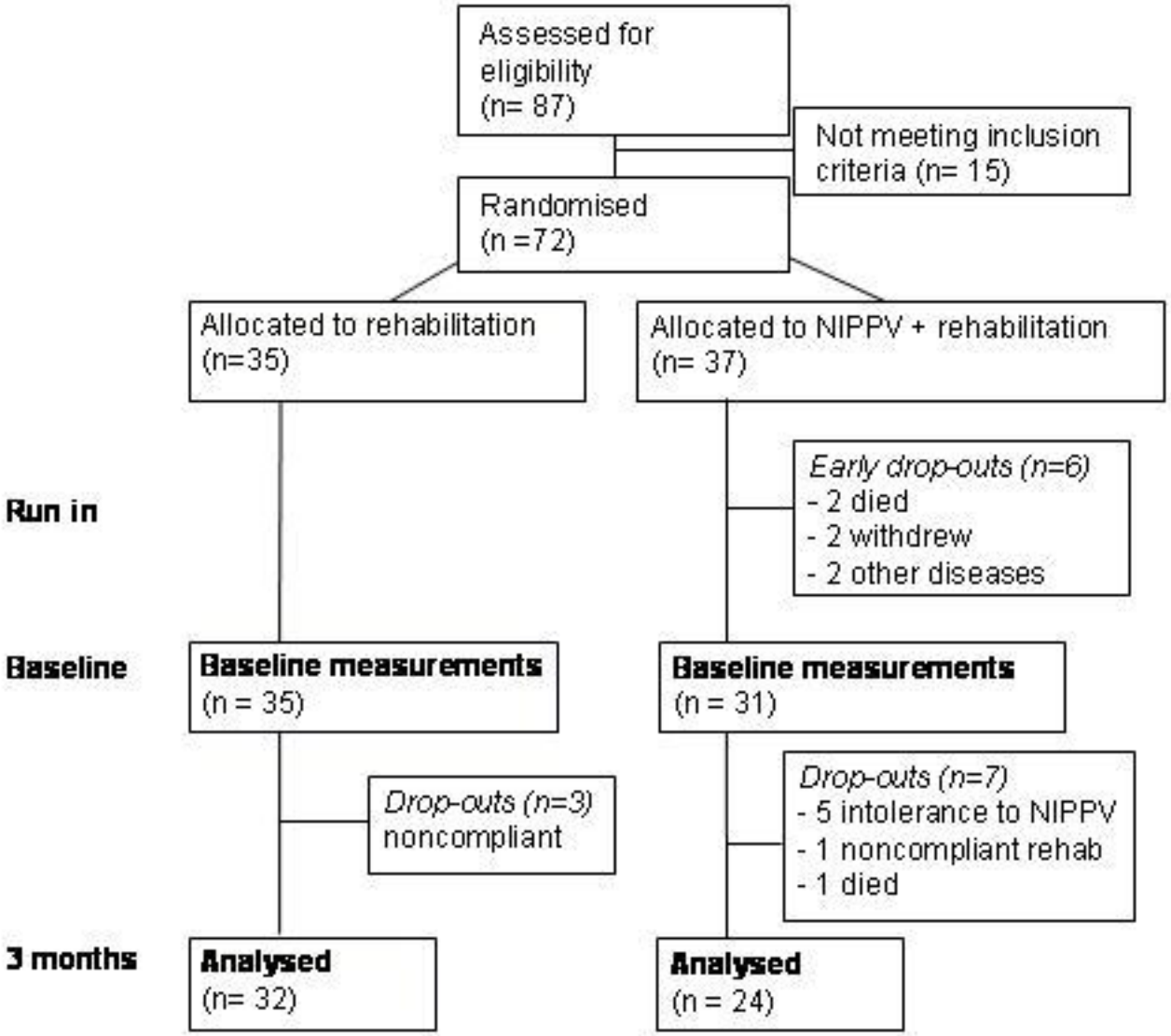
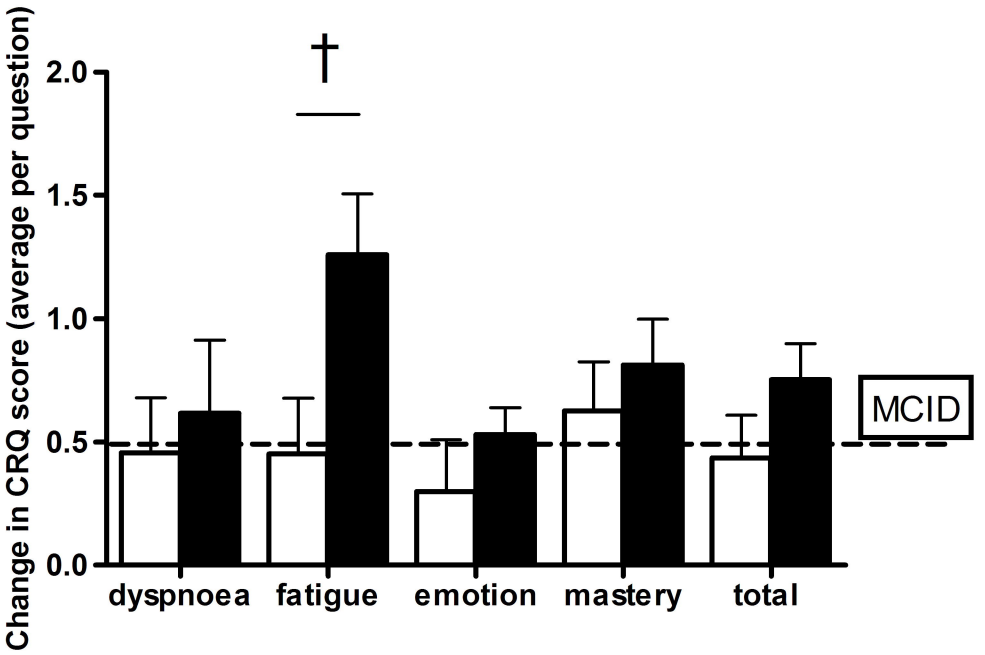
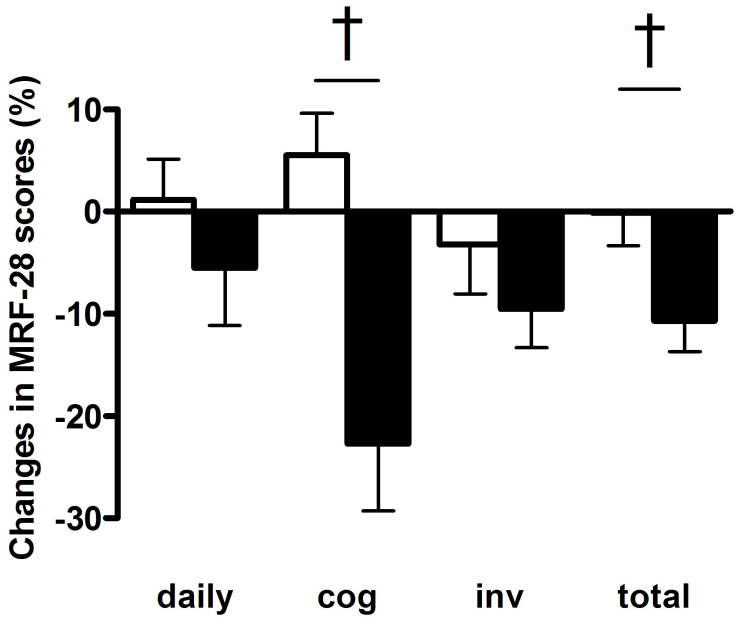
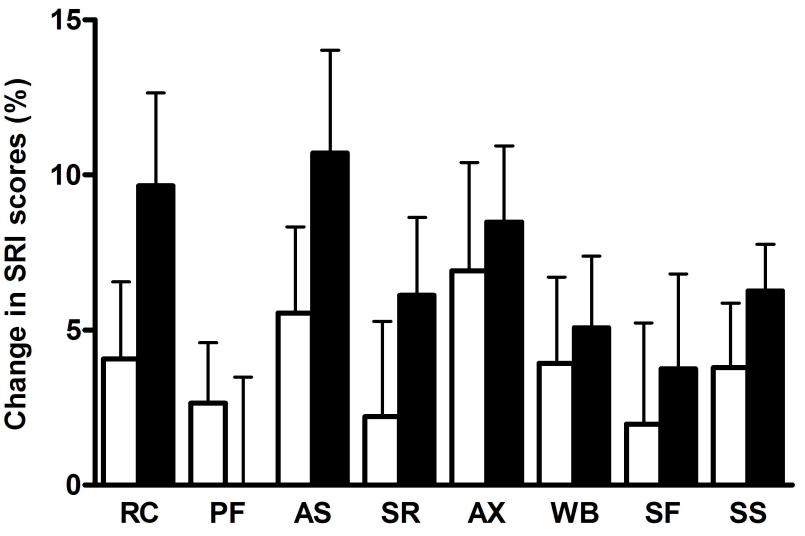



Change in CRQ score (average per question)
2.0
1.5
1.0
0.5
0.0
†
MCID
dyspnoea
fatigue
emotion
mastery
total


Changes in MRF-28 scores (%)
10
0
-10
-20
-30
†
†
daily
cog
inv
total


Change in SRI scores (%)
15
10
5
0
RC
PF
AS
SR
AX
WB
SF
SS

Daytime $PaCO_2$ at room air (kPa)
10
9
8
7
6
5
†
N+R: baseline
N+R: 3 months
R: Baseline
R: 3 months

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An overnight polygraphy (Embletta pds, Medcare Automation BV, Amsterdam, the Netherlands) was performed in patients with a body mass index ≥ 30 kg/m^2, in patients who snored or had complaints of disrupted sleep, excessive daytime sleepiness, or morning headache. Patients were excluded if the apnoea/ hypopnoea index was ≥ 10 episodes / hour. Of all 87 patients assessed for inclusion, a polygraphy was performed in 32 patients. The reason for performing the polygraphy was a BMI ≥ 30 in 25 patients, while a BMI <30 but complaints was the reason in seven patients. As shown in figure 1, 15 patients did not meet the inclusion criteria. In five of these 15 patients a polygraphy was performed. Four of them had an AHI-index> 10 and this was the reason for exclusion (median AHI-index 17.9 (range 15.0- 60.0 episodes/ hour)). The other 11 patients were excluded before because of an FEV_1>50% predicted or a PCO_2 < 6.0 kPa, cardiovascular disease, or an inability to fill in the questionnaires. Of the remaining 72 patients, a total of 16 patients dropped out (Figure 1). Of them, a polygraphy was performed in 4 patients (median AHI-index 3.2 (range 2.4- 6.0 episodes/ hour)). In the 56 completers, a polygraphy was performed in 23 patients (median AHI-index 2.0 (range 0.0- 9.8 episodes/ hour)).
Patients were excluded if medical history revealed significant cardiac diseases limiting exercise tolerance.
Therapy with long-term oxygen and medication was optimised during the intervention period by the pulmonary physician of the patient who was not involved in the study. Of the completers, 27 patients used long-term oxygen (LTOT) at baseline at a median flow rate of 1.5 L/min (range 0.5-3.0 L/min), at a median duration of 24 h/day (range 6-24 h/day). After 3 months, 32 patients were on LTOT, as 2 patients in the NIPPV+PR group and 4 patients in the PR group were prescribed LTOT during the rehabilitation period, while in one patient in the PR group LTOT was withdrawn because her resting PaO_2 without oxygen was 8.3 kPa. There were no significant differences in HRQoL scores between the patients on LTOT and the patients not on LTOT at baseline except for a higher MRF invalidity score in the LTOT patients (76 ± 28 % versus 57 ± 31%). Changes in HRQoL scores were not different except for a greater change in SRI physical functioning score in the patients not on LTOT (+ 6 ± 11 versus -3 ± 15 %). All arterial blood gas analyses were performed on room air without oxygen or ventilation.
At baseline, of the completers, 48 patients (86%) used inhaled corticosteroids, 26 patients (46%) used oral corticosteroids, 45 patients (80%) were on inhaled beta-agonist, 52 patients (93%) on anticholinergic medication, and 13 patients (23%) were on theophyllin. During the intervention period, in 3 PR patients, inhaled corticosteroids were started, in 1 PR patient oral steroids were started, in 3 PR patients beta-agonists were started, and in 2 PR patients anticholinergics were started. Additional changes in dose regimes were made by the patient's own pulmonologist.

Rehabilitation program

The participants followed a centre-based rehabilitation program of twelve weeks. The program could be followed in-hospital or as an out-patient, depending on travel distance to the centre. Nine rehabilitation centres in the northern part of the Netherlands participated. The program started with a 3-week period of upper and lower limb strength exercises (Enraf-Nonius, Rotterdam, the Netherlands), three times a week.[1] Thereafter, the program

continued with nine weeks cycling (Lode medical technology, Groningen, the Netherlands; Tunturi, Almere, the Netherlands), walking, and inspiratory muscle training (Threshold® IMT, Respironics**,** Murrysville, PA, US). The cycling was performed two times a week for thirty minutes according to an interval-based protocol.[2, 3]. This cycling protocol consisted of alternating 1 minute loaded cycling (aimed at 140% of a patients initial peak work rate on cycle ergometry), and 1 minute unloaded cycling, during a total of thirty minutes. Walking was performed twice a week. Initially patients walked ten minutes per session. Walking time was increased with five to ten minutes every week until the patients were able to walk thirty minutes per session. The speed of walking was adjusted in order to achieve a maximum Borg score of approximately 80% of the maximum Borg score at the initial six minute walking test. Inspiratory muscle training was performed on an inspiratory threshold device thirty minutes a day on an interval basis (2 minutes loaded breathing, followed by 1 min rest). The aim was to start with the threshold resistance on 30% of baseline maximal inspiratory pressure ($P_I$max). The resistance was increased with 5-10% per session until 70% $P_I$max was reached.[4, 5] Oxygen was used during training to maintain arterial oxygen saturation >92%. Twenty-nine patients used oxygen during the training (16 in PR group and 13 from NIPPV+PR group). The patients also participated in group education sessions where information was given about the disease, various strategies of treatment, use of medication, ways of coping with the disease, the role of rehabilitation, and how to recognise an exacerbation. Next to this, patients were taught breathing exercises, e.g. training lip-pursing techniques, expiratory abdominal augmentation, and synchronisation of thoracic and abdominal movement. Finally, patients received nutritional counselling by a dietician and, if necessary, psychosocial support.

NIPPV

Patients randomised to the NIPPV + rehabilitation group were instituted on NIPPV at the University Medical Center Groningen. They were hospitalised within a week after the baseline measurements and before the rehabilitation program started.
Non-invasive ventilation was supplied through a pressure cycled ventilator, applying both inspiratory and expiratory pressure to the patient (BiPAP; Synchrony, Respironics, INC., Murrysville, PA, USA). A nasal or full face mask (Mirage mask, ResMed Ltd, UK) of the proper size was used. The ventilator was set in a spontaneous/ time mode (S/T), with a backup frequency. We started with an inspiratory positive airway pressure (IPAP) of 12 cm H_2O and an expiratory positive airway pressure (EPAP) of 4 cm H_2O. IPAP was increased until the maximal tolerated pressure was achieved and titrated towards an optimal correction of arterial blood gases during the night ($PaCO_2$<6.0 kPa and a PaO_2>8.0). EPAP was titrated on patient comfort. Ventilator breathing frequency was adjusted to the patient's own spontaneous breathing frequency. If needed, O_2 was added to the ventilatory circuit to obtain a saturation of ≥ 90%. A humidifier (HC 150 Fisher & Paykel Healthcare, Australia) was used if needed. To monitor effectiveness of the NIPPV, nocturnal arterial blood gas registrations were performed in the intensive care unit at baseline before institution on NIPPV, after the practice period, and after three months. An arterial canula was placed in the a. radialis and arterial blood gas samples were taken every two hours. For analyses we used the mean of at least three samples taken when patients were asleep.
Initially, patients were hospitalised to practice NIPPV use under close supervision of a nursing consultant specialised in home mechanical ventilation. The in-hospital practice period lasted until patient could sleep at least six hours with the NIPPV (mean number of days necessary in our patients 5.0 ± 0.6 days). When a patient was able to sleep at least 6 hours per night with the ventilator, the second arterial blood gas registration was performed. If this gave satisfactory results, the patient went home with their ventilator. On the first day a home visit

was done by a specialised nursing consultant of the home mechanical ventilation centre, who supervised the ventilatory support during the whole study period. Ventilator compliance was determined from the ventilator counter readings.

Measurements

The following measurements were performed at baseline and after the 3-months intervention period.

Health-related quality of life

The primary outcome parameter was health-related quality of life, assessed by the interviewed version of the Chronic Respiratory Questionnaire (CRQ).[6] In addition, health-related quality of life was measured with the Maugeri Respiratory Failure questionnaire (MRF-28),[7] and the Severe Respiratory Insufficiency questionnaire (SRI).[8]

We used the interviewed version of the Chronic Respiratory Questionnaire (CRQ). It contains 20 items divided into four dimensions: dyspnoea, fatigue, emotion, and mastery. The CRQ total scores range from 20 to 140, with higher scores indicating better HRQoL. Physical function is assessed by asking the patients to quantify their dyspnoea during 5 frequently performed activities in daily life. They are asked to choose 5 activities from a list of 25 activities or they can mention activities not on the list. The CRQ dyspnoea domain scores range from 5 to 35. Physical function is also assessed by 4 items related to fatigue and energy level. The CRQ fatigue domain scores range from 4 to 27. Emotional function, including the emotion and mastery dimensions, includes questions about frustration, depression, anxiety, panic, and fear for dyspnoea. The CRQ emotion domain scores range from 7 to 49, those of the mastery domain range from 4 to 28.

The MRF-28 consists of 3 separate domains and a total score [7]. The daily activities domain contains 11 items related to dyspnoea during daily activities and impairments in daily activities. The cognition domain contains 4 items related to memory function, attention and concentration tasks. The invalidity domain contains 5 items on self-image, social functioning and relationships. Furthermore, the total score contains additional items related to fatigue, depression and problems with treatment, giving a total of 28 items. Scores are coded as 1 (patient agrees with the item) or 0 (patient does not agree). Scores are than recalculated as a percentage of items with which the patient agrees. MRF-28 scores range from 0-100, with higher scores indicating worse HRQoL [7].

The SRI contains 49 items divided in 7 subscales related to respiratory complaints (8 items), physical functioning (6 items), attendant symptoms and sleep (7 items), social relationships (6 items), anxiety (5 items), psychological well-being (9 items), social functioning (8 items), and a summary scale. Items are scores from 1 to 5, 35 items are then recoded, and the mean score is calculated to a percentage. SRI scores on each domain and the summary scale range from 0-100, with higher scores indicating better HRQoL [8].

Mood state

The hospital anxiety and depression scale (HADS) was used to assess mood state. It contains 7 items assessing anxiety and 7 items assessing depression [9]. Scores per item range from 0 (no anxiety/ no depression) to 3 (maximal anxiety/ depression). Separate anxiety and depression scores (ranging from 0-21) were obtained.

Dyspnoea

Dyspnoea was assessed by the Medical Research Council.[10] The MRC is a 5-point scale (1: only dyspnoeic during heavy exercise; 5: too dyspnoeic to leave the house) containing items on various physical activities that precipitate dyspnoea. Patients were instructed to read the descriptive statements and then select the statement which fitted best. Furthermore, prior to and during the exercise tests the subjects were asked to estimate dyspnoea intensity, using a 10-point modified Borg scale.[11]

Exercise tests

6-minute walking distance
A 6-minute walking test was performed indoors, along a 40-meter flat, straight corridor, with the turnaround point marked with a cone. All patients had performed a practice test during the run-in period. Patients used their usual walking aids and, if applicable, their usual ambulatory oxygen therapy during the test. The test assistant gave standardised encouragements every 30 seconds and told the patient after 2 and after 4 minutes that he/she was 2 and 4 minutes on his/her way.[12, 13]

Shuttle walk tests
All patients first performed an incremental shuttle walk test.[14] From this, endurance shuttle walk speed was determined according to the protocol of Revill.[15] First, maximal oxygen uptake (VO_2max) was calculated (VO_2max= (0.85*(4.19+0.025*incremental shuttle walk distance [14]). Thereafter, the correct endurance walking speed was read from the graph of endurance walking speed against VO_2max as presented by Revill.[15]
For both tests, a practice walk was done during the run-in period. Both tests were performed on a 10 m shuttle course on a quiet flat corridor, demarcated by cones inset 0.5 m from either end to compensate for turning points. Patients were instructed to walk along the course, turning around the cones at either end in synchronization with the audio signals from the cassette player. Prior to the test, patients were given standardized instructions about the tests and instructions to continue walking until too tired or breathless to continue. During the tests, the test operator sat alongside the course and no encouragements were given.
For the incremental shuttle walk test the modified protocol of Singh was used.[14] Each minute the walking speed was increased by 0.17 m/s, so that the patient was required to walk progressively faster. The end of the test was determined by a) the patient, when to exhausted to maintain the required speed; b) the operator, if the patients failed to reach the cone by > 0.5 m for a second time.[14]
For the endurance shuttle walk test, the same course was used. The test started with a "warm up" slower pace, which lasted for approximately 100 s, preceded the endurance speed to enable the patient to practice walking around the shuttle course. Thereafter the actual endurance speed started and remained constant for the whole test. The test ended if the patient indicated that he was too tired or too breathless to continue or if the cut off time at 20 minutes, chosen for practical reasons, was reached. However, patients were unaware of any time limit and were discouraged from estimating how long they had been walking. The patients performed the endurance shuttle walk test twice at baseline to exclude learning effects.[15] The better of these two tests was used for analyses.

Cycle ergometry
The bicycle tests were performed between 4 to 8 hours after switching from NIPPV to spontaneous breathing. Prior to the bicycle test, all patients received 400 microgram salbutamol to achieve optimal bronchodilatation.

First, daytime resting arterial blood gases on room air were taken from all patients while lying (Rapid lab type 865, Siemens, U.S.A.).
An incremental bicycle ergometry was performed using a 1-min incremental protocol. Patients were seated on the bicycle, respired through a mouthpiece and wore a nose clip during the test. During the whole test minute ventilation, tidal volume, breathing frequency, and oxygen uptake were measured continuously (Oxycon Pro, Viasys, Bilthoven, the Netherlands). First, recordings were made during breathing at rest for five minutes. The average values of these five minutes were used to analyse resting breathing patterns.
The exercise test started with 1 min unloaded pedalling at 60 cycles/min. This was followed by a 1-min incremental protocol at five watt load increment/min, until the patient reported exhaustion. The maximum workload was defined as the highest work level reached and maintained for a least thirty seconds.

Activities of daily living

Daily physical activity was assessed on a performance basis by the Digiwalker SW-200 (Yamax; Tokyo, Japan).[16-18] This pedometer has proved to accurately detect steps taken, as an indication of volume of daily physical activity.[16, 17, 19] It has also shown evidence of reliability and convergent and discriminative validity.[18] In this study, patients were instructed to wear the pedometer during ten days (until going to bed), and to record the number of steps per day. Steps/day was expressed as step equivalents.

Lung Function

All patients performed lung function testing post bronchodilatation with 400 microgram salbutamol. Vital capacity and forced expiratory volume in 1 second (FEV_1) were obtained by spirometry according to ERS criteria.[20] Out of a least three technically correct measurements, the highest value of at least two reproducible values was used (with ≤150 ml difference between those two measurements). Lung volumes, total lung capacity, functional residual capacity and residual volume, were measured by body plethysmography.[21] Furthermore, maximal inspiratory pressure ($P_I max$) was measured at residual volume after maximal expiration. The $P_I max$ manoeuvre was repeated at least five times with one minute rest between the measurements until 3 readings were obtained with less than 10% variance between the measurements. Pressures had to be maintained at least 1 second (Masterscreen PFT, Viasys, Houten, the Netherlands).[22]

RESULTS

Table 5. Changes in health-related quality of life scores after 3 months therapy

		Baseline	After 3 months	Change within group	Between group difference in change (95% CI)
Chronic Respiratory Questionnaire					
Dyspnoea, points	N+R	16.0 ± 4	19.1 ± 6	3.1	0.2 (-3.2 to 3.2)
	R	17.2 ± 5	19.5 ± 6	2.3	
Fatigue, points	N+R	13.8 ± 4	18.8 ± 4	5.0	3.3 (0.8 to 5.7) †
	R	13.6 ± 5	15.4 ± 6	1.8	
Emotion, points	N+R	32.6 ± 7	36.3 ± 6	3.7	2.4 (-0.9 to 5.5)
	R	30.7 ± 8	32.8 ± 8	2.1	
Mastery, points	N+R	19.3 ± 5	22.5 ± 4	3.3	1.5 (-0.4 to 3.4)
	R	17.8 ± 5	20.3 ± 5	2.5	
Total, points	N+R	81.7 ± 16	96.8 ± 15	15.1	7.5 (-1.0 to 16.0)
	R	79.3 ± 19	87.9 ± 20	8.7	
Maugeri Respiratory Failure Questionnaire					
Daily activities, %	N+R	58.9 ± 35	53.4 ± 29	-5.5	-5.3 (-17 to 6)
	R	55.7 ± 30	56.8 ± 27	1.1	
Cognition, %	N+R	50.0 ± 33	28.3 ± 25	-21.7	-22.0 (-35 to -9) †
	R	35.2 ± 39	40.6 ± 38	5.5	
Invalidity, %	N+R	67.0 ± 33	57.4 ± 33	-9.6	-6.1 (-19 to 7)
	R	65.0 ± 30	61.9 ± 36	-3.1	
Total, %	N+R	55.3 ± 24	44.6 ± 22	-10.7	-9.7 (-18 to -1) †
	R	52.2 ± 24	52.1 ± 24	-0.1	
Severe Respiratory Insufficiency Questionnaire					
Respiratory complaints, %	N+R	49.0 ± 17	58.7 ± 13	9.6	6.0 (-0.6 to 12.0)
	R	48.1 ± 17	52.1 ± 17	-4.1	
Physical functioning, %	N+R	40.9 ± 18	40.9 ± 21	0	-2.3 (-9.7 to 5.1)
	R	39.3 ± 17	42.0 ± 18	2.6	
Attendant symptoms and sleep, %	N+R	60.4 ± 19	71.1 ± 16	10.7	7.4 (-0.6 to 15.3)
	R	54.6 ± 18	60.2 ± 20	5.5	
Social relationships, %	N+R	58.4 ± 17	64.5 ± 13	6.1	1.0 (-5.6 to 7.6)
	R	63.3 ± 16	65.5 ± 14	2.2	
Anxiety, %	N+R	54.8 ± 23	63.3 ± 17	8.5	3.1 (-5.1 to 11.3)
	R	50.7 ± 20	56.9 ± 22	6.1	
Well-being, %	N+R	63.0 ± 19	68.1 ± 14	5.1	4.2 (-2.5 to 10.9)
	R	54.9 ±20	58.8 ±19	3.9	
Social functioning, %	N+R	50.3 ± 21	54.1 ± 16	3.7	1.1 (-6.4 to 8.6)
	R	51.6 ± 20	53.6 ± 18	2.0	
Summary score, %	N+R	53.8 ± 15	60.1 ± 11	6.3	3.1 (-2.0 to 8.2)
	R	51.8 ±14	55.7 ±15	3.8	

Legend table 5: Means ± SD scores. N+R: NIPPV+ rehabilitation versus R: rehabilitation alone. *: denotes significant change from baseline to 3 months within the group; †: denotes significant difference in change between groups.

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